REMARKS

Reconsideration of this application is requested.

Obvious errors in the specification have been corrected.

Claims 39, 40 and 43 have been canceled. The claims pending for consideration are prior claims 1-38, 41, 42, 44-48 and new claims 49-86.

The pending claims may be grouped as follows:

(1) Claims 1-29 and new claims 58-68 and 73-76 are drawn to oral dosage forms comprising proton pump inhibitor (PPI) and H2 receptor antagonist with excipient(s) such as to provide delayed and/or extended release of the PPI and rapid release of the H2 receptor antagonist. As discussed below, the applicants' position is that it is unobvious to combine a PPI and H2 antagonist as claimed as and for the purpose indicated in claim 1. Claims 2-29, claims 58-68 and 73-76 are dependent on claim 1, directly or indirectly, and bring in preferred subsidiary features of the invention. The features of these claims are thought to add separate patentability in the context of a composition according to claim 1.

(2) Claims 30-38 are drawn to the method of preparing the applicants' compositions. Of these claims, claim 30 is the applicants' main claim while claims 31-38 depend therefrom. There is no suggestion in the art of the applicants' preparation method as described in any of claims 30-38.

(3) Claims 41, 42 and 44-57 and new claims 69-72 and claims 77-86 are directed to methods of using the applicants' composition of claim 1. Claims 41 and 42 call for the use of the dosage form of claim 1 for the treatment of a condition associated with the secretion of gastric acid (claim 41) or the treatment of an infection of Helicobacter pylori (claim 42). Other dependent claims such as claims 44-47 are drawn to prepared method features which, like claims 41 and 42, are also not suggested by the prior art. Certain of the method claims call for use of the method "on demand" (e.g. claim 49) while others are specific to the treatment of infection by Helicobacter pylori (e.g. claims 42, 52 and 71). Some of the method claims, i.e. claims 69-72 and 79-86, call for the use of two separate dosages, one containing the PPI and the other the H2 receptor antagonist, administered concomitantly.

All of the applicants' claims are thought to be allowable over the prior art, including the references relied on by the Examiner as there is nothing in the art suggesting the use in combination, whether separately or together in a common dose, of a PPI and H2 receptor antagonist, with delayed and/or extended release and with rapid release, respectively, for the

treatment of a condition associated with the secretion of gastric acid or for the treatment of infection by Helicobacter pylori.

New claims 49-86 find support throughout the applicants' disclosure. For example, the "on demand" feature of claim 49 is supported by the applicants' disclosure at page 10, 1st ¶, while claim 50 represents a combination of claims 41, 2 and 4. Claim 51 is similar to claim 50 but also brings in the "on demand" feature disclosed at page 10, 1st ¶.

Claim 52 combines features of claims 2, 4 and 42 while claims 53 to 57 depend from claim 51 and bring in features of claims 44 to 48, respectively.

Claim 58 combines features of claims 1, 2 and 4 and claims 59 and 60 are drawn to features of claims 12 and 13, respectively, with different dependence. Claims 61-86 also include features of other claims with different dependency.

The applicants submit that all of the claims herein including those newly added are in acceptable form and otherwise allowable for reasons noted below.

The Examiner is requested to reconsider the provisional Section 101 rejection based on the claims in Appln. No. 11/544,750. The claims of Appln. No. 11/544,750 are being amended in response filed simultaneously herewith so as to be different from the claims as presented herein. Accordingly, it is believed that rejection under Section 101 is not appropriate. The applicants are, however, prepared to file a Terminal Disclaimer with respect to Appln. No. 11/544,750 if the Examiner deems this to be necessary.

Reconsideration of the Section 112, 2nd ¶ rejection of claims 25-29, 39 and 40 is requested in view of the foregoing amendments to the claims. Claims 39 and 40 have been canceled and claims 24-29 amended in a way which is thought to obviate the basis for the Examiner's objection to these claims.

Other changes have been made in the claims which are thought to improve the form thereof.

The Examiner is respectfully requested to reconsider the Section 103(a) rejection of claims 1-39, 41, 43 and 44 as unpatentable over Saslawski et al. (WO 99/33448) in view of H. Hedenström et al. With respect, it is submitted that these references, no matter how considered, do not make the applicants' invention obvious.

As understood, it is the Examiner's position that Saslawski et al. (hereinafter '448) discloses the concept of using multiple active agents such as ranitidine, famotidine and omeprazole in multilayered formulations wherein a first layer provides for immediate release and a second inner layer provides a sustained release. Hedenström is cited as showing that

pH recitations in the applicants' claims are inherently met by the use of high doses of active ingredients according to the art. The Examiner acknowledges certain deficiencies in '448 (¶s 13, 14 of the action) but takes the position that the applicants' features in this regard represent routine experimentation, are within the level of skill for one in the art at the time the invention was made and, therefore, obvious.

The applicants respectfully submit that their invention, as defined by the rejected claims, is not obvious from the cited references. A fundamental deficiency in the Examiner's position is an apparent lack of appreciation that one of ordinary skill in the art at the time of the applicants' invention, would not have considered it desirable to use a PPI and an H2 receptor antagonist together because the conventional thinking would be that one of these agents (the H2 antagonist) would prevent the other (the PPI) from functioning.

As stated in the applicants' disclosure (page 10, 1st ¶), the invention is particularly useful in the "on demand" treatment of gastro-esophageal reflux (GERD) complaints, such as heartburn, which are disorders associated with dyspepsia.

As noted at page 1, lines 21-25 of the applicants' disclosure, dyspepsia is a common disorder. In the US alone, around 25% of the total adult population experiences heartburn at least weekly.

The symptoms of heartburn/GERD occur acutely and are at best uncomfortable and at worst extremely painful. It is, therefore, important that patients obtain immediate relief from such symptoms and for that relief to be sustained for as long as those symptoms continue. Nevertheless, prior to the present invention, there was a clear unmet clinical need for a rapidly acting, potent and sustained acid-reducing medicament for the symptomatic treatment of these conditions. The present invention effectively deals with this unmet need.

In terms of the most widely prescribed treatments for gastrointestinal disorders generally, prior to the present invention, H2 receptor antagonists were known to be capable of giving rise to a rapid onset of action and, therefore, fast relief of symptoms (see the Introductory section of Hedenström et al. However, it was also known that H2 receptor antagonists would give rise to the phenomenon of tolerance (a tendency to fade during prolonged treatment; see, for example Hurliman et al, ibid., 8:193 (1994) first paragraph, left-hand column, page 194 (of record). PPIs, on the other hand, were known to take several days to build up to a satisfactory degree of acid inhibition (see again Hurliman, *supra*, top of left-hand column, page 194), but were known to exhibit a better effect over the long term. In

this respect, neither H2 receptor antagonists nor PPIs alone solve the problem of providing, for example, an on-demand, rapid and potent effect that is also sustained for as long as is required by, for example, dyspepsia patients. Furthermore, and of particular importance in considering the patentability of the applicants' invention, H2 antagonists and PPIs were considered incompatible for use in combination therapy (in the manner herein claimed) because of the understood mechanisms of action of PPIs and H2 receptor antagonists. This is evident from a consideration of Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 10th Edition, a textbook which is highly regarded by those in the pharmaceutical field. Particularly relevant to the present case is Goodman et al. Chapter 37 (by Hoogerwerf et al.) a copy being of record. More specifically, Goodman et al. note (see page 1007) that PPIs **as a class** require acid to be activated and perform their function. According to Goodman et al, acid is produced in parietal cells in the gastric mucosa by the enzyme H^+,K^+-ATPase (also known as the proton pump):

> "[PPIs] are...benzimidazoles...; their pharmacological properties are similar. [PPIs] are 'prodrugs', requiring activation in an acid environment. These agents enter the parietal cells from the blood and, because of their weak basic nature, accumulate in the acid secretory canaliculi of the parietal cell, where they are activated by a proton-catalyzed process that results in the formation of a thiophilic sulfonamide or sulfenic acid. This activated form reacts by covalently binding with the sulfhydryl groups of cysteines from the extracellular domain of the H^+,K^+-ATPase. Binding to the cysteine 813, in particular, is essential for inhibition of acid production, which is irreversible for that pump molecule...".

As stated in Goodman et al., towards the end of the right-hand column at page 1009, H2 receptor antagonists on the other hand:

> "...inhibit acid production by reversibly binding to H_2 receptors on the basolateral membrane of parietal cells".

Thus, both classes of compounds inhibit the production of acid at the parietal cell level, in the case of H2 receptor antagonists by rapidly blocking receptors on the baso-lateral cell surface to give rapid relief to patients, and in the case of PPIs by a slow process that involves accumulation in acid and acid-catalyzed chemical conversion to an active form that gradually switches off the enzyme responsible for acid secretion.

Because H2 receptor antagonists rapidly reduce the amount of acid in the parietal cell, it follows that there would be less acid in that environment to accumulate and activate PPIs to enable them to exert their effect. Indeed, this clearly was the perceived wisdom in the art prior

to the applicant's invention, as evidenced by Goodman et al. *supra* at the first full paragraph at page 1009, where it is unequivocally stated that:

> "The requirement for acid to activate these drugs [PPIs] within parietal cells has several important consequences....coadministration of other acid-suppressing agents **such as H2 receptor antagonists** may diminish the efficacy of [PPIs]".

In short, any skilled person in the relevant art would have been abundantly aware of, this clear and unambiguous teaching in the art at the time the present invention was made and would not think to even attempt to **simultaneously** co-administer H2 receptor antagonists and PPIs, because the former would be expected to diminish the effect of the latter.

The applicants submit that the foregoing comments from Goodman et al. effectively show that the applicants' combination of PPI and H2 receptor antagonist to use in the treatment of a condition associated with the secretion of gastric acid or in the treatment of an infection of Helicobacter pylori as called for in the applicants' claims would not be obvious.

The applicants do not take issue with the Examiner's construction of '448 in terms of, in a general sense, the structure of the formulations that are taught therein. However, the applicants do not agree that it would have been obvious from '448 to employ, in a specific sense, an H2 receptor antagonist in the outer (immediate release) layer and a PPI in the inner (sustained release) layer, both from the point of view of what is taught in '448 and from what was known in the art at the relevant time as discussed in detail above.

Although it is stated at page 4, lines 12 and 13 of '448, that different active ingredients may be employed in separate layers of the '448 formulations, it is thereafter stated that, as a clearly preferred feature:

> "*...according to a specific embodiment of the invention, the first and second layers comprise the* ***same*** *active substance"* (emphasis added).

This preference is also shown in claim 2 of '448 which specifies that the active ingredient employed in the respective layers is identical. Thus, at least in a preferred sense, '448 does not teach a combination of different active agents.

Furthermore, it is noted that '448 lists, over nearly five pages (page 4, line 21 to page 9, line 29), a plethora of different possible active ingredients that may be employed. This is essentially nothing more than a textbook listing of many known groups of pharmaceutically active agents and there is clearly nothing in '448 suggesting that PPI and an H2 receptor antagonist should be singled out for use together from the massive listing of compounds referred to in '448.

Thus, it is clearly a preferred teaching of '448 to employ a single active ingredient and the skilled person would not be motivated by '448 to employ different drugs (of **any** nature) in the bilayer formulation described in the reference to arrive at a "combination" product. Furthermore, even if different drugs are selected, there is no pointing to the applicants' specific combination of PPI and H2 receptor antagonist.

The specific active ingredients that are referred to by the Examiner are mentioned in '448, in no particular order but only as part of a very long list of possible drug candidates that might be employed in the '448 formulation. It is respectfully submitted that, even if a skilled person were motivated to employ two different drugs in the separate layers of '448, there is not even the remotest suggestion in '448 to employ two different active ingredients from the same activity class (as opposed to two compounds from different active classes), let alone from within the same "antiulcer drug" class. Furthermore, and most importantly, in the unlikely event that a skilled person were to employ two different active ingredients from the same, antiulcer class, they would **not** select one of the H2 receptor antagonists mentioned in '448 as one component and a PPI, e.g. omeprazole, as the other. This would mean going in a diametrically opposite direction to the general teaching in the art at the relevant time, as discussed in detail above.

The applicants submit that the skilled person would be doing something unobvious going beyond the teaching of the art to combine an H2 receptor antagonist in the outer, immediate release layer, and a PPI in the inner, sustained release layer to arrive at something approaching the invention claimed in the present application. Thus, in summary, the applicants submit that no information is provided by '448 that would motivate the skilled person to go against the common general knowledge that was well known in the art and arrive at the invention claimed in the present application.

Furthermore, Hedenström does not fill in the substantive deficiencies of the '448 disclosure. More specifically, Hedenström discloses a study in which intragastric pH is compared in healthy volunteers receiving either H2 receptor antagonists, such as ranitidine and famotidine, **or** the PPI, omeprazole. Thus, there is no suggestion in Hedenström to combine H2 receptor antagonists and PPIs in any fashion, let alone concomitantly, in the manner claimed in the present application. This is, of course, entirely consistent with the wisdom in the art at the time, which was, as discussed above, **not** to co-administer H2 antagonists and PPI in a concomitant fashion.

For reasons indicated, the applicants submit that claims 1-39, 41, 43 and 44 (now claims 1-38, 41, 43 and 44) distinguish unobviously and, therefore, patentably from '448 and Hedenström. Accordingly, reconsideration and withdrawal of the Section 103(a) based on '448 and Hedenström et al. are requested.

For essentially similar reasons, the Examiner is requested to reconsider and withdraw the Section 103(a) rejection of claims 1, 40, 42 and 45-58 based on '448 and Hedenström considered with Gshwantler et al. The last-mentioned reference does not fill in the indicated deficiencies of '448 and Hedenström. Gschwantler compares Helicobacter pylori in infected ulcer and/or dyspepsia patients receiving different drug regimens (famotidine or omeprazole) in combination with antibiotics clarithromycin and metronidazole. There is clearly no suggestion in Gshwantler to combine an H2 receptor antagonist and a PPI for the purposes disclosed and claimed by the applicants.

The applicants submit for the reasons noted that their prior claims 1-38 and 41-48 should be allowable. For similar reasons, the applicants submit that their new claims 49-86 should be allowable.

Favorable reconsideration, with allowance is requested. The Examiner is requested to telephone the undersigned should any questions or unresolved issues arise.

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

Paul N. Kokulis, Reg. No. 16,773

Date: October 29, 2007

Customer No. 09629
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Phone: (202) 739-3000
Facsimile: (202) 739-3001
Direct: (202) 739-5455